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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,603	FERRARA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/7/03; 7/22/03; 5/6/02; 4/2/02;*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *19, and 25-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,20-24 and 62-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/25/02;* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-79 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-11, 14-18 and 22-24 (now claims 1-18, 20-24, and 62-79) drawn to antagonist antibody and composition comprising said antibody, filed 11/7/03, is acknowledged. The request that (1) the new claims including linking claims should been retained in the application and considered once the claims in Group I are allowable and (2) Upon allowance of any of the linking claims (New claims 62 and 63), additional species of antagonist such as small molecule, peptide fragment and antisense molecules be examined is acknowledged. Upon reconsideration, claims 12-13, 20-22 and 62 that read on an antagonist of an EG-VEGF polypeptide have been rejoined with Group I which drawn to antagonist EG-VEGF polypeptide wherein the antagonist polypeptide is antagonist antibody. Therefore, the requirement of Group I (now claims 1-11, 14-18, 20-24, and 62-79) and Groups 2-34 is still deemed proper and is therefore made FINAL.

3. Claims 19, and 25-61 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-18, 20-24, and 62-79 are being acted upon in this Office Action.

5. Claim 11 is objected to for reciting non-elected embodiment.

6. The disclosure is objected to because of the following informalities: (1) "Figures 11A-**B**" on page 9, line 23 does not match with the actual drawing (Figure 10A-C). It should be "Figure 10A-C"; (2) "Figure 20A-P" on page 12, line 19 should have been "Figure 20A-Q". (3) "F(ab□)$_2$" on page 74, line 5 should have been "(Fab')$_2$. Appropriate action is required.

7. Claims 11, 14, 17 and 63 are objected to as the claims encompass non-elected embodiments.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-18, 20-24, and 62-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the monoclonal antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 4H9.1A7.1H6, 1C6, 2A3, 2A8 and 4H9 in claims 1-10, 15-16, 23-24 and 70-73 are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.

If it is not so obtainable or available, a deposit of hybridomas secreting said monoclonal antibodies may satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See 37 CFR 1.801-1.809.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required.

Applicants are reminded that the current address of the ATCC is as follows and should amend the specification accordingly:

American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridomas secreting said antibodies have been deposited under the Budapest Treaty and that the hybridomas will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or **for the enforceable life of the patent whichever is longer**. See 37 CFR 1.806.

If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate

the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which case the statement need not be verified. See MPEP 1.804 (b).

Further, the specification does not provide sufficient guidance for (1) *any* anti-EG-VEGF antibody such as 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 4H9.1A7.1H6, 1C6, 2A3, 2A8 and 4H9, (2) *any* antibody such as chimeric antibody, humanized antibody, human antibody, bispecific antibody, and fragment thereof that binds essentially to the same epitope of EG-VEGF bound by any antibody selected from the group consisting of anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, (3) *any* labeled antibody such as chimeric antibody, humanized antibody, human antibody, bispecific antibody, and fragment thereof that binds essentially to the same epitope of EG-VEGF bound by any antibody selected from the group consisting of anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, or any bispecific antibody having binding specificity for VEGF, (4) any composition of matter comprising any antagonist of any EG-VEGF polypeptide, any EG-VEGF polypeptide is any native sequence EG-VEGF, any human EG-VEGF, any antagonist anti-EG-VEGF antibody, any anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, (5) any composition comprising any antibody and fragment thereof that binds essentially to the same epitope of EG-VEGF bound by any antibody selected from the group consisting of anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, (6) *any* composition mentioned above further comprising any VEGF, or any agonist or any antagonist thereof, any VEGF is any native VEGF polypeptide, or any human VEGF polypeptide, (7) *any* article of manufacture as set forth in claim 23-24, (8) *any* antagonist of EG-VEGF polypeptide wherein the antagonist inhibits *any* EG-VEGF polypeptide induced proliferation of adrenal cortex-derived endothelial cell, *any* antagonist of EG-VEGF polypeptide is *any* antibody such as any chimeric antibody, *any* single chain antibody, *any* bispecific antibody, *any* humanized antibody, any polyclonal, any monoclonal antibody and fragment thereof, *any* small molecule, *any* peptide fragment, or *any* antisense molecule, *any* EG-VEGF polypeptide is a native sequence of EG-VEGF, *any* native human EG-VEGF, any EG-VEGF polypeptide comprises any amino acid sequence having at least about 80% identity to SEQ ID NO: 2, *any* amino acid sequence "comprises" amino acid residues 20 to 105 or any amino acid residues from x to 105 wherein x is from 14 to 24 of SEQ ID NO: 2 for treating any disease or

any condition associated with infertility, *any* condition associated with polycystic ovary syndrome, or cancer.

The specification discloses only four monoclonal antibodies 1C6, 2A3, 2A8 and 4H9 that bind specifically to human EG-VEGF comprising SEQ ID NO: 2 as shown in Figure 21 for diagnostic assays. The specification further discloses that only monoclonal antibodies 1C6 and 4H9 have neutralizing activity in cell-based proliferation assays (See Figure 21, see error bar).

The specification does not teach how to make any antibody mentioned above because there is insufficient guidance as to the immunogen (biochemical properties and amino acid sequence) used by applicant to make any EG-VEGF antibody, or any antibody that has antagonist activity to *any* EG-VEGF polypeptide, let alone antibody that binds substantially to the epitopes of undisclosed antibodies such as 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6. Further, there is insufficient guidance as to binding specificity of the claimed antibody. The term "essentially the same epitope of EG-VEGF" is not defined in the specification. Further, the specification discloses only 1C6, 2A3, 2A8 and 4H9 as shown in Figure 21 for diagnostic assays and not "1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6" as claimed. Given the indefinite number of undisclosed antibody, EG-VEGF and without the specific amino acid sequence, it is unpredictable which undisclosed antibody would bind specific to EG-VEGF, let alone antibody that binds essentially the same epitope as antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6, in turn, would be useful for any purpose.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Since the binding specificity of the claimed antibody is not enabled, it follows that any antibody fragment, chimeric antibody, humanized antibody, bispecific antibody, labeled antibody are not enabled. It also follows that any composition or article of manufacture comprising any undisclosed antibody mentioned above are not enabled.

With regard to antagonist of EG-VEGF polypeptide is any small molecule, peptide fragment and antisense molecule, the term "small molecule", "peptide fragment" and "antisense molecule" without the specific amino acid sequence or nucleotide sequence have no structure, much less function.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Given the indefinite number of "small molecule", "peptide fragment" and "antisense molecule", there is insufficient guidance and working example demonstrating that any "small molecule", "peptide fragment" and "antisense molecule" have antagonist function toward any EG-VEGF. There is insufficient guidance and working example as to how to make and to how to use any EG-VEGF antagonist which blocks *any* EG-VEGF activity as encompassed by the claims. The specification as filed has not provided sufficient biochemical information such as amino acid composition, N-terminal sequence, etc on the small molecule, peptide fragment, and antisense molecule that distinctly identifies the specific antagonistic activity. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 18 24 (CCPA 1970). Since the amino acid sequence of a molecule/polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a molecule's structure and still retain similar functionality (antagonistic activity) requires a knowledge of and guidance. However, the problem of predicting the epitope to which undisclosed antagonist antibody binds is complex and outside the realm of routine experimentation. The more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. See MPEP 2164.03.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser,

Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document). Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Because applicants have not disclosed. There is insufficient guidance for any antagonist EG-VEGF polypeptide that has 80% identical to SEQ ID NO: 2 and has antagonist activity. A 20% differences in SEQ ID NO: 2 is 21 amino acids difference. Further, the term "comprises" is open-ended. It expands the amino acid sequence having 20% difference to include additional amino acids at either or both ends. Not only the antagonist polypeptide is not enable, it is not clear which epitope on the undisclosed EG-VEGF polypeptide having 20% difference that the claimed antagonist antibody binds.

With regard to claims 78-79, the term "comprises" is open-ended. There is insufficient guidance for the undisclosed amino acid residues to be added at either or both ends of the antagonist polypeptide comprises amino acid residues 20 to 105 or X to 105 of SEQ ID NO: 2 wherein X is amino acid residues from 14 to 24 of SEQ ID NO: 2. It is unpredictable which undisclosed EG-VEGF polypeptide would maintain the same structure and function as SEQ ID NO: 2, and whether the claimed antibody that binds to said undisclosed EG-VEGF polypeptide has antagonist activity.

Given the indefinite number of undisclosed antagonist polypeptide and antagonist antibody and without the specific amino acid residues, it is unpredictable which undisclosed EG-VEGF antagonist would bind specifically to EG-VEGF, much less having antagonistic activity, in turn, would be useful for treating *any* condition. Further, there is a lack of *in vivo* working example demonstrating *any* composition mentioned above are effective for treating *any* disease such as diabetes, infertility, polycystic ovary syndrome, or cancer.

Fogarty *et al* teach targeting angiogenesis using VEGF antagonist is a promising anticancer approach, however, the twelve recent failures in clinical trials using VEGF antagonist, indicate the unpredictability of angiogenesis inhibitors for cancer treatment.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-18, 20-24, and 62-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* anti-EG-VEGF antibody such as 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 4H9.1A7.1H6, 1C6, 2A3, 2A8 and 4H9, (2) *any* antibody such as chimeric antibody, humanized antibody, human antibody, bispecific antibody, and fragment thereof that binds essentially to the same epitope of EG-VEGF bound by any antibody selected from the group consisting of anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, (3) *any* labeled antibody such as chimeric antibody, humanized antibody, human antibody, bispecific antibody, and fragment thereof that binds essentially to the same epitope of EG-VEGF bound by any antibody selected from the group consisting of anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, or any bispecific antibody having binding specificity for VEGF, (4) any composition of matter comprising any antagonist of any EG-VEGF polypeptide, any EG-VEGF polypeptide is any native sequence EG-VEGF, any human EG-VEGF, any antagonist anti-EG-VEGF antibody, any anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, (5) any composition comprising any antibody and fragment thereof that binds essentially to the same epitope of EG-VEGF bound by any antibody selected

from the group consisting of anti-EG-VEGF antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7, and 4H9.1A7.1H6, (6) *any* composition mentioned above further comprising any VEGF, or any agonist or any antagonist thereof, any VEGF is any native VEGF polypeptide, or any human VEGF polypeptide, (7) *any* article of manufacture as set forth in claim 23-24, (8) *any* antagonist of EG-VEGF polypeptide wherein the antagonist inhibits *any* EG-VEGF polypeptide induced proliferation of adrenal cortex-derived endothelial cell, *any* antagonist of EG-VEGF polypeptide is *any* antibody such as any chimeric antibody, *any* single chain antibody, *any* bispecific antibody, *any* humanized antibody, any polyclonal, any monoclonal antibody and fragment thereof, *any* small molecule, *any* peptide fragment, or *any* antisense molecule, *any* EG-VEGF polypeptide is a native sequence of EG-VEGF, *any* native human EG-VEGF, any EG-VEGF polypeptide comprises any amino acid sequence having at least about 80% identity to SEQ ID NO: 2, *any* amino acid sequence "comprises" amino acid residues 20 to 105 or any amino acid residues from x to 105 wherein x is from 14 to 24 of SEQ ID NO: 2 for treating any disease or *any* condition associated with infertility, *any* condition associated with polycystic ovary syndrome, or cancer.

The specification discloses only four monoclonal antibodies 1C6, 2A3, 2A8 and 4H9 that bind specifically to human EG-VEGF comprising SEQ ID NO: 2 as shown in Figure 21 for diagnostic assays. The specification further discloses that only monoclonal antibodies 1C6 and 4H9 have neutralizing activity in cell-based proliferation assays (See Figure 21, see error bar). Further, the specification discloses only one EG-VEGF from human comprising amino acid residues 1-105 of SEQ ID NO: 2.

With the exception of the specific monoclonal antibodies 1C6, 2A3, 2A8 and 4H9 that bind specifically to EG-VEGF comprising SEQ ID NO: 2 and the specific antagonist antibodies 1C6 and 4H9 that have neutralizing activity in cell-based proliferation assays, the binding specificity of the monoclonal antibody such as 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6 is not adequately described. Further, the immunogen used by applicants such as amino acid sequence and the binding specificity of the claimed antibody have been adequately described. Since the binding specificity of the claimed antibody is not adequately described, it follows that the composition comprising the undisclosed antibody for treating any disease is not adequately described.

With regard to "essentially the same epitope bound by an antibody", the term "essentially the same epitope of EG-VEGF bound by the antibody" is not defined in the specification. Not

only the epitope of EG-VEGF to which the antibody such as 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6 bound is not adequately described, it is not clear what is meant by "essentially the same" since the term "essentially" is not defined in the specification.

With regard to antagonist of EG-VEGF polypeptide is any small molecule, peptide fragment and antisense molecule, the term "small molecule", "peptide fragment" and "antisense molecule" without the specific amino acid sequence or nucleotide sequence have no structure, much less function. Further, there is inadequate written description about the binding specificity of any antibody such humanized, chimeric, single chain, human antibody and fragment thereof mentioned above for treating any condition. Further, the specification disclosed only one human EG-VEGF comprising SEQ ID NO: 2, the antagonist polypeptide to any EG-VEGF is not adequately described.

With regard to claims 78-79, the term "comprises" is open-ended. There is inadequate written description about the undisclosed amino acid residues to be added at either or both ends of the antagonist polypeptide that comprises amino acid residues 20 to 105 or X to 105 of SEQ ID NO: 2 wherein X is amino acid residues from 14 to 24 of SEQ ID NO: 2 and whether the claimed antibody would bind specifically to said undisclosed EG-VEGF polypeptide and maintains antagonist activity to any EG-VEGF.

Given the lack of a written description of *any* additional representative species of antagonist polypeptide, any antagonist polypeptide is any EG-VEGF antibody as encompassed by the claims for treating any disease, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. Claims 1-10, 15-16, 23-24, and 70-73 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6" in Claims 1, 2, 15, 16, 23, 24, and 70-73 represents a departure from the specification and the claims as originally filed. The specification discloses only four monoclonal antibodies 1C6, 2A3, 2A8 and 4H9 that bind specifically to EG-VEGF as shown in Figure 21 for diagnostic assays.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 1-10, 15-16, 23-24, 65, and 70-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6" in claims 1, 2, 16, 23, 24, 70-73 is ambiguous and indefinite because said 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6 are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct antibodies. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "monoclonal antibodies" in claim 1 ambiguous and indefinite because the plural antibodies do not matched with the antibody in the preamble (An antibody).

The "essentially the same epitope bound by an antibody" in claims 2, 16, and 23 is ambiguous and indefinite because the specification does not defined said term "essentially". Further, it is not clear which epitope is essential. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The "antibody fragment" in claims 3, 17, and 65 have no antecedent basis in base claims 2, 11, and 64, respectively. It is suggested to amend base claim 1 to provide antecedent basis for said phrase. For example, An antibody or fragment thereof that binds specifically to EG-VEGF comprising SEQ ID NO: 2 wherein the antibody is 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 or 4H9.1A7.1H6 (claim 1). It is also suggested that claim 3 be amended to recite "The antibody or fragment thereof of claim 1 wherein the antibody is an antibody fragment".

The "which is human" in claim 7 is erroneous. It is suggested that claim 7 be recite "The antibody or fragment thereof of claim 2 wherein the antibody is a human antibody". Likewise, claims 5-6 and 8 should also be amended in the same way as indicated above.

The "which is detectably labeled" in claim 10 lacks antecedent basis in base claim 2. It is suggested that the claim be rewritten to "A labeled antibody or fragment thereof wherein the antibody or fragment thereof of claim 2 is detectably labeled".

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 2, 7, 10-14, 16, 18, 20-22, 62-64, 68-69, 74-76 and 78-79 are rejected under 35 U.S.C. 102(b) as being anticipated by Brekken *et al.* (Cancer Research 58(9): 1952-59; May 1998; PTO 892).

Brekken *et al* teach various antagonist antibodies such as monoclonal antibody 3E7, GV39M, 11B5 and 2C3 and polyclonal antibody A-20 that binds specically to VEGF:receptor complex or VEFG itself (See abstract, page 1953, hydridoma, control antibodies, in particular). The reference antibody 2C3 is a monclonal antibody that binds to free human VEGF and thereby inhibitig VEGF binding to the VEGF receptor VEGFR2 (KDR/Flk-1) without significantly inhibiting VEGF binding to the VEGF receptor VEGFR1 (Flt-1) (See page page 1953, second and third paragraphs; Table 1 on page 1954; Fig 1; page 1954, left column, lines 8-9 and lines 21-23; page 1957, left column, second paragraph, line 14-17; page 1956, right column second paragraph, line 1, in particular). Brekken *et al* teach a composition comprising the reference antibody and a pharmaceutical acceptable caririer such as PBS (See page 1953, first column, antibody purification, in particular). The reference composition further comprises a native human VEGF sequence (See page 1953, column 1, competition ELISA experinment, in particular). Brekken *et al* further teach that the reference antibody is labeled (See Materials and Methods, page 1953, column 1 last paragragraph, in particular). However, the binding specificity and the epitope on EG-VEGF to which the claimed antibody binds appears to include the reference antibodies as described by Brekken *et al.* The recitation of "1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6" in claims 1, 2, 16, 23, 24, 70-73 appear to bind "essentially the same epitope" as the reference antibody 2C3 because the reference antibody 2C3 VEGF:receptor complex or VEGF itself. Therefore the claimed antibody appears to be the same as the prior art antibody. Since the Patent Office does not have the facilities for examining and comparing the

antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Claims 76, 78-79 are included in this rejection because the term "comprising" is open-ended. It expands the amino acid seuqence of EG-VEGF to include the reference human VEGF polypeptide to which some of the reference antibodies bind. Thus, the reference teachings anticipate the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 2-4, 11, 17-18, 62 and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken *et al* (Cancer Research 58(9): 1952-59; May 1998; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629).

The teachings of Brekken *et al* have been discussed supra.

The claimed invention in claims 3, 17 and 65 differs from the teachings of the reference only that the antibody is a antibody fragment.

The claimed invention in claims 4, 18 and 66 differs from the teachings of the reference only that the antibody is a Fab, Fab', and $F(ab)_2$.

Harlow *et al* further teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* further teach

that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment as taught by Harlow *et al* with the antagonist VEGF antibody as taught by Brekken *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular).

19. Claims 2, 5-7, 62, 64 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken *et al* (Cancer Research 58(9): 1952-59; May 1998; PTO 892) in view of US Pat No. 6,180,370B (of record, filed June 1995; PTO 892).

The teachings of Brekken *et al* have been discussed supra.

The claimed invention in claims 5 and 67 differs from the teachings of the reference only that the antibody is a chimeric antibody.

The claimed invention in claims 6 and 67 differs from the teachings of the reference only that the antibody is a humanized antibody.

The claimed invention in claim 7 differs from the teachings of the reference only that the antibody is a human antibody.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular). The said chimeric antibody comprises a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody as taught by the '370 patent that that binds essentially to the same epitope of EG-VEGF bound by antibody taught by taught by Brekken *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce chimeric antibody because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

20. Claims 2, 8-9, 62, 64 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken *et al* (Cancer Research 58(9): 1952-59; May 1998; PTO 892) in view of US Pat No 6,132,729 (Oct 2000, PTO 892).

The teachings of Brekken *et al* have been discussed supra.

The claimed invention in claims 8 and 67 differs from the teachings of the reference only that the antibody is a bispecific antibody.

The claimed invention in claims 9 and 67 differs from the teachings of the reference only that the bispecific antibody has binding specificity for VEGF.

The '729 patent teaches that the preparation of bispecific antibody having the specificity of desired targets for tumor treatment is well known in the art and is useful for against diverse tumor targets (See column 74, lines 42-52, column 75-76, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce bispecific antibody as taught by the '729 patent that that binds essentially to the same epitope of EG-VEGF bound by antibody and VEGF as taught by Brekken *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce bispecific antibody because the '729 patent teach that bispecific antibody having the specificity of desired targets for tumor treatment is well

known in the art and is useful for against diverse tumor targets (See column 74, lines 42-52, column 75-76, in particular).

21. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken *et al* (Cancer Research 58(9): 1952-59; May 1998; PTO 892) in view of U.S. Pat No. 5,858,682 (filed Aug 1996, PTO 892; see entire document).

The teachings of Brekken *et al* have been discussed supra.

The claimed invention in claim 23 differs from the teachings of the reference only that an article of manufacture (kit) comprising a container, label and comprising an anti-EG-VEGF antibody that bind essentially the same epitope as an antibody selected from the group consisting of monoclonal antibodies 1C6.1H6.1D7, 2A3.1C5.1F3, 2A8.1H4.1E7 and 4H9.1A7.1H6.

The '682 patent teaches a kit (article of manufacture) comprising an antibody for diagnostic assays (See column 3, line 40; column 6, line 17; column 8, line 36, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in a kit taught by the '682 for the antagonist antibody as taught by Brekken et al for diagnostic assays as taught by the '682 patent. One would have been motivated, with a reasonable expectation of success, to place the antibody taught by Brekken in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '682 (See column 8, line 36-57, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

22. Claims 2-4, 11, 17-18, 62, and 64-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken *et al* (Cancer Research 58(9): 1952-59; May 1998; PTO 892) in view of US Pat No. 4,946,778 (of record, PTO 892).

The teachings of Brekken *et al* have been discussed supra.

The claimed invention in claims 4, 18 and 66 differs from the teachings of the reference only that the antibody is Fv fragments.

The claimed invention in claim 67 differs from the teachings of the reference only that the antibody is single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody or a polypeptide fragment (Fv fragment) (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce single chain antibody as taught by the '778 patent that binds essentially to the same epitope of EG-VEGF bound by antibody taught by taught by Brekken *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce single chain antibodies because the '778 patent teaches that the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

25. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

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